**Conditional power analysis of the DEBUT trial**

Yang Wanga, Tao Chenb, Sidong Lia, Yanyan Zhaoa, Wei Lia

*aMedical Research & Biometrics Center, National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

*bTropical Clinical Trials Unit, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, L3 5QA, UK*

Correspondence author: Wei Li

Medical Research & Biometrics Center, National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Room 101-106, BLOCK A Feng Cun Xi Li, Yongding Zhen Mentougou District Beijing, 102300, China

E-mail: WeiLi@mrbc-nccd.com

Funding Sources: None.

Recent results from a single-blind, randomised, non-inferiority trial in patients with de-novo coronary artery lesions and at high bleeding risk, reported a significantly deceased incidence of major adverse cardiac events in the group treated with drug-coated balloon.1 In this study, the absolute difference of primary outcome at 9 months was reported as -13.2% ([95% CI -6.2 to -21.1]). The authors therefore claimed that percutaneous coronary intervention with drug-coated balloon was superior to bare-metal stent in patient at bleeding risk; on the contrary, we believe the conclusion should be interpreted with cautions.

It should be noted that the original planned sample size of 534 in DEBUT study was 80% power to show non-inferiority with 1-sided 0.05 alpha and 3% non-inferiority margin. However, there was an extra 3% treatment benefit on assumed effect size (7% vs. 10% in drug-coated balloon and bare-metal stent group respectively) during the calculation. If under a flat event rate assumption ( i.e., 10% in both groups), the overall sample size required will increase to 2474 patients. More important, there were no pre-specified interim analysis plan and corresponding stopping rules in their registered protocol (NCT01791546). In fact, the DEBUT study was prematurely terminated at 220 subjects due to slow patient recruitment

The current study had a p<0.00001 for non-inferiority and p=0.00034 for superiority. Those p-values were much lower than the thresholds determined by major approaches of alpha-spending function.2 however, conditional power (CP) is much more important, even though the authors calculated the post-hoc power for group difference (97.5%) based on observed data. CP refers to the probability of concluding a positive study at the end of trial, given the interim results of treatment effect and the distribution of future response.3 Table 1 shows CPs under different scenarios of assumed treatment effect. Non-inferiority hypothesis could be supported in most situations. For example, the CP could achieve 91.6% if the event rate equals among the future unenrolled patients. However, the CPs for superiority were unacceptable low if no absolute difference favor drug-coated balloon on estimated proportion of major adverse cardiac events (i.e., scenario 3 and 4), which are reasonable assumptions, particularly, the long-term safety of paclitaxel-coated balloons and stents has become a concern for femoropopliteal artery intervention. Overall, we strongly agree with the authors that further randomised controlled trials are needed to ascertain the findings from DEBUT study.

**References:**

1. Rissanen TT, Uskela S, Eranen J et al. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk (DEBUT): a single-blind, randomised, non-inferiority trial. *Lancet*. 2019;394(10194):230-239

2. Discrete Sequential Boundaries for Clinical Trials Author(s): K. K. Gordon Lan and David L. DeMets Source: Biometrika, Vol. 70, No. 3 (Dec., 1983), pp. 659-663 Published by: Biometrika Trust Stable URL: http://www.jstor.org/stable/2336502 . Accessed: 18/06/2014 17:53.

3. Flexible interim analysis method for sample size re-estimation and early stopping: a conditional power approach.

Table 1 Conditional power under different scenarios with assumed treatment effects for future responses

|  |  |  |  |
| --- | --- | --- | --- |
| Scenarios | Assumed between group effect size(DCB vs. BMS)\* | CP (%) by calculation# | CP (%) by simulation@ |
| For non-inferiority | For superiority | For non-inferiority | For superiority |
| 1 | 1% vs. 14% | 100.0 | 100.0 | 100.0 | 100.0 |
| 2 | 7% vs. 10% | 99.8 | 90.4 | 99.3 | 85.1 |
| 3 | 10% vs. 10% | 97.1 | 63.1 | 91.6 | 46.9 |
| 4 | 13% vs. 10% | 83.9 | 30.3 | 65.4 | 14.9 |

\* DCB – drug coated balloon, BMS – bare-metal stent. CP: Conditional power.

# The calculated CPs were calculated from the join-distribution of the observed data from 220 recruited patients and the assumed data from 314 subjects without recruiting (planned 534 minus 220 enrolled).

@ The individual level data were generated for the 220 enrolled and 314 future patients under observed and assumed effect size, separately, using Monte Carlo random simulation . The CPs were obtained from this pooled data set.